DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

M466N

JUN 26 1998

Transmitted Via Facsimile

Mr. Howard Solomon
President and CEO
Forest Laboratories, Inc.
909 Third Avenue
New York, NY 10022-4731

Re: NDA 18-340
Aerobid/Aerobid-M (flunisolide) Inhaler System
MACMIS ID 5792

WARNING LETTER

Dear Mr. Solomon:

This Warning Letter concerns Forest Laboratories, Inc.'s (Forest) promotion of Aerobid/Aerobid-M (flunisolide) Inhaler System. Based on information the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed as part of our routine monitoring and surveillance program, we have concluded that Forest has disseminated promotional materials that contain false or misleading statements or suggestions that Aerobid has a superior safety profile compared to competitive products in violation of 21 USC §§ 352(a), 331(a) of the Federal Food, Drug, and Cosmetic Act and applicable regulations, including, but not limited, to 21 C.F.R. § 201.6(a).

A. Introduction

Forest's activities represent a highly organized and orchestrated campaign to disparage the safety of a competitive orally inhaled corticosteroid, Flovent (fluticasone propionate) Inhalation Aerosol, marketed by Glaxo Wellcome, Inc. Through various marketing mechanisms, Forest disseminated false or misleading safety information about Flovent to state or suggest that Flovent presents a safety risk because of systemic absorption, as measured by cortisol suppression, in asthma patients who are treated with various total daily doses of Flovent.[1] Forest's dissemination of these false or misleading

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[1] Flovent Inhalation Aerosol is manufactured and marketed in three dosage strengths: 44 mcg, 110 mcg, and 220 mcg.

representations suggests that Forest's Aerobid has a superior safety profile. However, in the absence of substantial evidence comparing these products, Forest's claims are unsupported and misbrand Aerobid. A sponsor misbrands its own drug product by making false or misleading representations about another product in its labeling. 21 C.F.R. § 201.6(a).

FDA has evaluated the potential systemic effects of inhaled Flovent on the hypothalamic-pituitary-adrenal or HPA-axis, as described in the Flovent approved product labeling. In controlled clinical trials, no patient taking Flovent at doses of 220 mcg twice daily (for a total daily dose of 440 mcg) for four weeks had an abnormal morning cortisol response to stress as assessed by ACTH/6-hour cosyntropin stimulation. Ten percent (10%) to 16% of Flovent treated patients at doses of 440 mcg or more twice daily had an abnormal response. Therefore, contrary to Forest's concerted violative promotional activities misrepresenting Flovent's safety, this measure of potential systemic effect has been accurately and publicly disclosed in Flovent's approved product labeling.

B. Forest's Promotional Activities

Over the past several years, Forest has engaged in targeted promotional activities that falsely or misleadingly question the safety of Flovent in an effort to promote Aerobid and to convince health care providers to switch patients from Flovent to Aerobid. These promotional activities and materials include, among others, the following:

1. Dissemination of Forest's sponsored "5-way" study abstract reprint.

2. Dissemination of Forest's sponsored "National Cortisol Testing Program" (NCTP) data results.

3. Presentation of Forest's sponsored and controlled teleconferences to physicians entitled, "Systemic Effects with Inhaled Steroids and the Potential for Osteoporosis".

1. 5-Way Study Abstract Reprint

In an untitled letter dated, November 21, 1996, DDMAC objected to Forest's dissemination of a misleading study abstract and its data to promote Aerobid that compared the systemic effects of five inhaled corticosteroids, including Flovent. The abstract, referred herein as the "5-way" study, was entitled "A five-way parallel randomized study to compare the safety profile of flunisolide, fluticasone propionate,

beclomethasone dipropionate, budesonide, and triamcinolone acetonide in healthy male volunteers". Forest used the 5-way study to suggest that Aerobid is safer than competitive orally inhaled corticosteroids, particularly Flovent, as signaled by cortisol suppression or HPA-axis effects. DDMAC objected to the dissemination and use of this information as inadequate to support a claim of superior safety because of a variety of methodological deficiencies. These deficiencies include the use of non-U.S. formulations of the compared drug products and the use of single doses that, because of varying systemic potencies of the five products, lack comparable efficacy upon which to base safety comparisons. Because of these false or misleading messages, DDMAC requested that Forest stop using these materials to promote Aerobid.

On January 21, 1997, DDMAC met with Forest to discuss this issue. Thereafter, Forest submitted and DDMAC reviewed a revised proposed promotional brochure featuring the 5-way study reprint, including the disclaimers Forest added to the introduction and conclusion. Notwithstanding the proposed disclaimers, the overall false or misleading suggestion presented in the reprint was that Aerobid is safer than competitive oral inhaled corticosteroids, particularly Flovent. In a March 3, 1997, letter, DDMAC notified Forest that it would consider any dissemination of the proposed revised promotional material to be violative of the Act. However, Forest has continued to disseminate these violative promotional materials.[2] This subsequent violative conduct reflects Forest's intent to disparage Flovent's safety profile. Such action misbrands Aerobid through Forest's false or misleading promotional claims alleging Aerobid's superiority safety.

2. National Cortisol Testing Program/NCTP

In a 1997 promotional campaign to present negative product information about the safety of Flovent, Forest sponsored, conducted, and disseminated misleading representations via its "National Cortisol Testing Program" (NCTP). DDMAC has received information that demonstrates that the NCTP was, in fact, a promotional program to support its inhaled steroid product, Aerobid.

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[2] DDMAC has information that Forest may have promoted the results of the 5-way study through various forums, including, but not limited to: (1) disseminating the abstract reprint to individual physicians and in exhibit halls of annual health care professional conferences; (2) issuing a press release in which Forest described the study and suggested that the study demonstrates that Aerobid has a superior safety profile to the compared products; (3) organizing a speakers series, through a public relations firm, to present the study to health care practitioners; and (4) organizing teleconferences in which the study was presented to health care practitioners.

The NCTP solicited and engaged physicians to take blood samples from up to four asthma patients treated with varying doses of Flovent. According to Forest's plan, these blood samples were to be analyzed for cortisol suppression as a surrogate marker of systemic absorption. However, the NCTP was inadequate in design and conduct to produce any meaningful information. The use of an open-label design with no control arm or baseline measurement prior to initiation of Flovent therapy could not substantiate Forest's claims that cortisol suppression occurred with the use of Flovent at various total daily doses. Therefore, Forest's express or implied promotional claims concerning the potential effects of Flovent therapy on cortisol suppression/HPA-axis function, or differences between Flovent and Aerobid, based on NCTP data were not supported by substantial evidence.

Moreover, the NCTP was portrayed to participating physicians as independent clinical research throughout the solicitation, conduct, and distribution of the program's results and claims. Although Forest sales representatives delivered the NCTP kits to physicians and encouraged the physicians' participation in the program, Forest did not identify itself as the sponsor of the program in any of the NCTP-related materials. The laboratory study kit was processed by Laboratory Corporation of America (LabCorp) and the NCTP test results were distributed to participating physicians in the form of "Dear Doctor Letters" on NCTP letterhead. The suggestion that this program was an independent national program and the lack of disclosure about Forest's sponsorship may have led physicians to a greater and unequivocal acceptance of the false or misleading messages disseminated by Forest.

Thus, through the NCTP, as with the 5-way study, Forest developed and disseminated a promotional program that disparaged a competitive product by suggesting that the product's use in asthma patients presents a safety risk because of systemic absorption. Such false or misleading representations about a competitive product misbrands Aerobid.

3. Forest's Teleconferences entitled "Systemic Effects with Inhaled Steroids and the Potential for Osteoporosis"

On various dates in 1997[3], Forest sponsored a promotional teleconference program to health care practitioners entitled "Systemic Effects with Inhaled Steroids and the Potential for Osteoporosis." The program included slides and materials distributed to participants containing numerous false or misleading statements or suggestions about Aerobid and Flovent concerning systemic safety. Although the program was described as "systemic effects with inhaled steroids..." the predominant focus of the program, through presentation of both flawed noncomparative and comparative data, was to suggest that Flovent was not systemically safe and, by implication, that Aerobid had superior safety.

Among the materials Forest disseminated for the teleconferences was the violative 5-way study discussed above, as well as other sources of false or misleading information. For instance, an abstract of a study by Dempster et al., supported by Forest and entitled "Effects of Fluticasone Propionate (FP) on Plasma Cortisol and Osteocalcin Levels," was presented. The stated objective of this study was "to assess the correlation of HPA-axis suppression with an established marker of bone formation, osteocalcin." The abstract concludes that Flovent, dosed at 880 mcg twice daily for a total daily dose of 1,760 mcg, is highly suppressive on cortisol and osteocalcin and that HPA-axis suppression and osteocalcin suppression are highly correlated.

However, the study suffers from various methodological deficiencies that make it inadequate to substantiate safety claims about Flovent or Aerobid. First, the study used only a small number of healthy volunteers, rather than a reasonably large enough sample of asthmatic patients. Second, only one dose of Flovent was examined and therefore no dose-response relationship (correlation) to HPA-axis or other systemic effects could have been demonstrated. Third, the only dose of Flovent examined (a high dose of 880 mcg twice daily) was approved for weaning asthma patients from systemic (oral prednisone) corticosteroids, and any systemic effects present with transfer to high-dose orally inhaled Flovent from oral prednisone are significantly less than with prednisone. And finally, although osteocalcin may be "an established marker of bone formation" it is unclear whether a change in osteocalcin, particularly for such a short time period, is clinically significant.

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[3] Some of the dates upon which these teleconferences occurred in 1997 were: July 28, August 12 and 14, September 30, and October 8.

C. Conclusions and Requested Actions

Forest's activities have resulted in the dissemination of false or misleading information about Glaxo Wellcome's drug product Flovent Inhalation Aerosol, as well as Forest's drug product Aerobid. Accordingly, Forest should propose an action plan, including the mailing and dissemination of a "Dear Healthcare Professional" letter, in order to disseminate corrective messages about the issues discussed in this letter to all healthcare providers, institutions, and organizations who received the violative messages, or who were solicited to participate in the NCTP.

The action plan should include:

1. The immediate cessation by Forest, LabCorp, or any other agent of Forest, of dissemination of all materials: based on results from the NCTP or other sources, that falsely or misleadingly disparages the safety profile of Flovent through measurement of cortisol suppression or other systemic effects, or that falsely or misleadingly suggest that Aerobid is superior in safety to Flovent, unless such claims are supported by substantial evidence.

2. A written statement of Forest's intent to comply with "A" above.

3. The dissemination, within 15 days of the date of this letter, of a message to all Forest sales representatives and marketing personnel involved in the marketing and sales of Aerobid/Aerobid-M Inhaler System, instructing them to immediately cease dissemination of all promotional materials and messages discussed in this letter and providing each person with a copy of this letter.

Forest's action plan and "Dear Health Care Professional" letter should be submitted to DDMAC for approval. After such approval, the action plan should be implemented as soon as possible.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of Forest's promotion of Aerobid and we may determine that additional remedial measures will be necessary to fully correct the false or misleading messages resulting from Forest's violative conduct.

Forest's response should be received no later than July 13, 1998. If Forest has any questions or comments, please contact Joan Hankin, J.D., Norman Drezin, J.D., or Thomas Abrams, R.Ph., M.B.A., by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm 17-B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Forest that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS ID 5792 and NDA 18-340.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

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Minnie Baylor-Henry, R.Ph., J.D.
Director
Division of Drug Marketing,
Advertising, and Communications